

Chapter 4

S_N2 Substitution Reactions

As alluded to in previous chapters, the study of organic chemistry requires an understanding of the mechanistic types that drive reactions. While the detailed mechanisms associated with some complex reactions may lie beyond the scope of an introductory organic chemistry course, the fundamental components are easily recognized and applied to the reactions contained within generally presented curricula. As stated in earlier discussions, this book presents the concept of arrow pushing with a focus on heterolytic reaction mechanisms. However, it is important to remember that the lessons presented herein are applicable to organic chemistry regardless of the mechanistic type.

While the fundamental mechanistic components of organic chemistry can be combined to describe complex mechanisms associated with complex reactions, the individual mechanistic components fall into a relatively small and well-defined group of four. These are **S_N1**, **S_N2**, **E1**, and **E2** reactions. In this chapter, the fundamentals associated with **S_N2** reactions are presented.

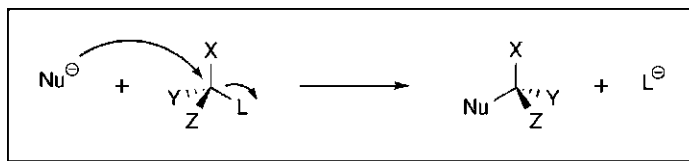
4.1 WHAT IS AN S_N2 REACTION?

Among the mechanistic types relevant to organic chemistry, the **S_N2** reaction mechanisms are the simplest. In progressing from starting materials to products, these reactions generally consist of a nucleophile displacing a leaving group. As illustrated in Scheme 4.1, consider a molecule where L^- is a leaving group. As shown, a nucleophile, Nu^- , can be introduced with displacement of the leaving group, thus generating a new molecule.

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.

By Daniel E. Levy

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Scheme 4.1 Representation of an S_N2 reaction.

While discussions of **stereochemistry** are left to the organic chemistry textbooks adopted for introductory classes, it is important to recognize the **stereochemical** implications of S_N2 reactions. In this respect, molecular bonds are drawn with either a straight line, a wedge, or a hashed wedge. Bonds drawn with straight lines are understood to lie in the same plane as the two-dimensional page on which they are drawn. Bonds drawn with wedges are understood to project above the plane of the page on which they are drawn. Finally, bonds drawn with hashed wedges are understood to project below the plane of the page on which they are drawn.

Recognizing that the substituents residing on a tetra-substituted carbon atom are spherically spaced equidistant from one another, if all substituents are connected with lines, a **tetrahedron** is formed. Furthermore, as shown in Figure 4.1, if all four substituents are unique, they can be arranged in two configurations where the two molecules are mirror images and not superimposable. Because these two molecules are identical in composition but not configuration in three-dimensional space, they are referred to as

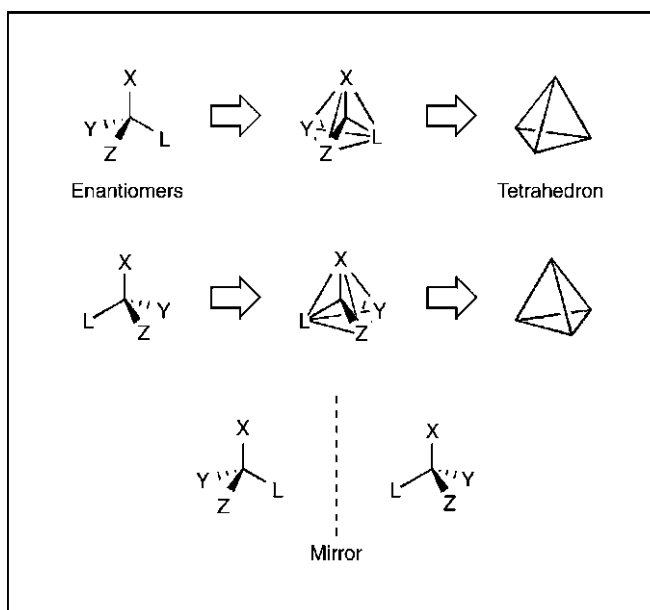
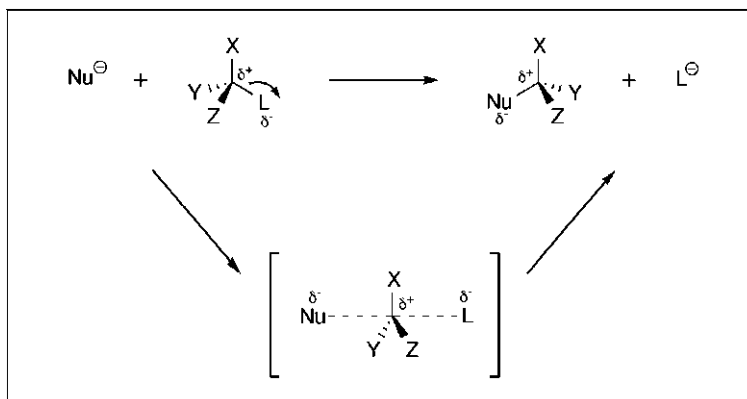


Figure 4.1 Enantiomers are mirror images, not superimposable, and dependent upon the tetrahedral arrangement of carbon atom substituents.



Scheme 4.2 Mechanistic explanation of S_N2 reactions.

stereoisomers. Furthermore, when two molecules differ only by the spatial arrangement of their substituents rendering them mirror images of each other, these molecules are called **enantiomers.**

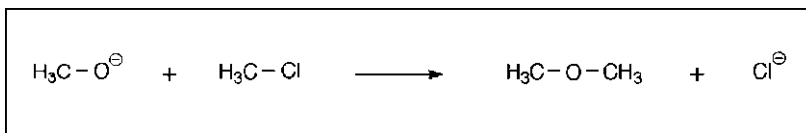
The above discussion of stereochemistry is important to the context of S_N2 reactions because, as illustrated in Scheme 4.1, when a nucleophile displaces a leaving group, the **configuration** of substituents X, Y, and Z with respect to L becomes inverted. Thus, the configuration of X, Y, and Z with respect to Nu is opposite to their configuration with respect to L. As shown in Scheme 4.2, this **inversion** of configuration is mechanistically explained through the simultaneous formation of the Nu–carbon bond and cleavage of the L–carbon bond. Elongated hashed lines are used to illustrate the partial formation or cleavage of molecular bonds. Electronically, this mechanism is explained with the placement of partial positive and partial negative charges.

Looking at Scheme 4.2, we recognize that an S_N2 reaction proceeds with the Substitution of a leaving group with a Nucleophile leading to the S_N designation. Because this mechanism proceeds with the initial approach of two species, it is referred to as a bimolecular reaction. The involvement of 2 species enhances the mechanistic designation to S_N2.

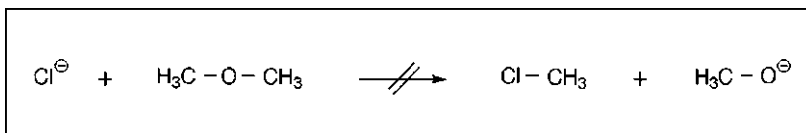
4.2 WHAT ARE LEAVING GROUPS?

The concept of leaving groups was introduced in Chapter 3 and presented in the context of nucleophiles and acid–base chemistry. However, with respect to S_N2 reactions, there are additional perspectives, relating nucleophiles to leaving groups, deserving attention. For example, in the context of **nucleophilic substitution** reactions, it is reasonable to conclude that leaving groups are nucleophiles. In fact, this is generally true, and one requirement for a nucleophilic substitution reaction to proceed is that the incoming nucleophile be a better nucleophile than the leaving group.

In consideration of the relationship between nucleophiles and leaving groups, recall that the pK_a values for methanol are 15–16 and the pK_a value for hydrochloric acid is –2.2. Because methanol is less acidic than hydrochloric acid, methoxide ions are expected to be better nucleophiles than chloride ions. This is, in fact, the case and the



Scheme 4.3 S_N2 reactions proceed when incoming nucleophiles are more nucleophilic than outgoing leaving groups.



Scheme 4.4 S_N2 reactions do not proceed when incoming nucleophiles are less nucleophilic than outgoing leaving groups.

S_N2 reaction illustrated in Scheme 4.3 will proceed to completion. Furthermore, as illustrated in Scheme 4.4, the reverse reaction will not proceed because relative to chloride ions, methoxide ions are poor leaving groups.

In summary, S_N2 reactions are defined by the principles surrounding organic acids and their conjugate bases as discussed in Chapters 2 and 3. Specifically, as discussed in Chapter 3, relative nucleophilicities can be estimated based on pK_a values. Finally, relative pK_a values can be used to predict whether a reaction will proceed and what component of the starting material will be the leaving group.

4.3 WHERE CAN S_N2 REACTIONS OCCUR?

With an understanding of what S_N2 reactions are, it is now important to understand where, on a given molecule, such reactions will take place. The answer to this question can be found by recognizing electronegativity trends. As previously discussed, an atom's electronegativity relates to how strongly it holds on to its electrons. This translates into greater partial negative charges residing on more electronegative atoms and smaller partial negative charges residing on less electronegative atoms. Regarding trends, as previously discussed, relative electronegativities of atoms are readily identified using the periodic table of the elements. For example, moving across each row of the periodic table, we find that electronegativity increases among the atoms, thus indicating that oxygen is more electronegative than nitrogen and that fluorine is more electronegative than oxygen.

As discussed in previous chapters, pK_a values are directly related to electronegativities. This is clearly reflected in the nitrogen–oxygen–fluorine trend discussed above, considering that amine pK_a values are approximately 35, alcohol pK_a values are approximately 15–19, and the pK_a value for hydrofluoric acid is approximately 3. The increase in acidity is related to increased electronegativity because more electronegative atoms are more stable in their anionic form. Thus, fluorine can stabilize a negative charge better than oxygen, which, in turn, can stabilize a negative charge better than nitrogen.

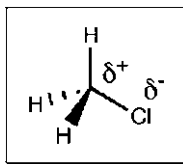


Figure 4.2 Chloromethane bears a partial negative charge on the electronegative chlorine atom and a partial positive charge on the carbon atom.

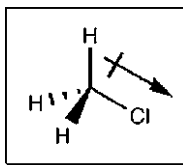


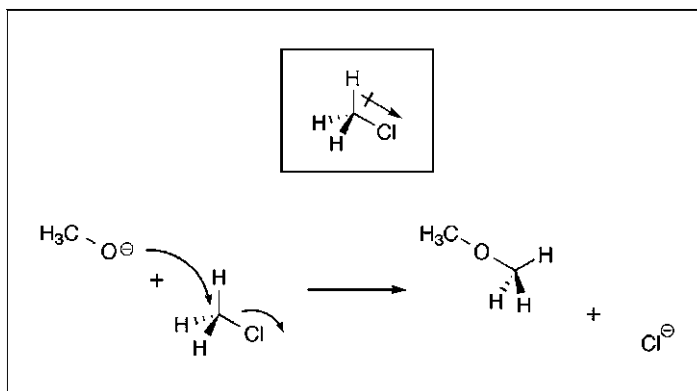
Figure 4.3 The carbon–chlorine bond in chloromethane is polarized.

Since nucleophiles, by definition, are attracted to positively charged centers, we must consider how such centers become attractive to nucleophiles. This effect relates to the electronegativity of the atoms attached to the center. Since an electronegative atom retains a partial negative charge, the electronegative atom pulls electron density from the atom on which it resides (usually carbon), leaving it with a partial positive charge. This effect is illustrated in Figure 4.2 where an electronegative chlorine atom is attached to carbon and inducing a partial positive charge.

When a bond joins an atom bearing a partial positive charge to an atom bearing a partial negative charge, the bond is said to be polarized. Much in the same way a magnet possesses a positive pole and a negative pole, the respective ends of a **polarized bond** are positively and negatively charged. When referring to polarity and polarized bonds, the direction of polarity is, by convention, from positive to negative. As shown in Figure 4.3, this is commonly illustrated using a special arrow with a + at the positive end and the tip pointing in the direction of the negative end.

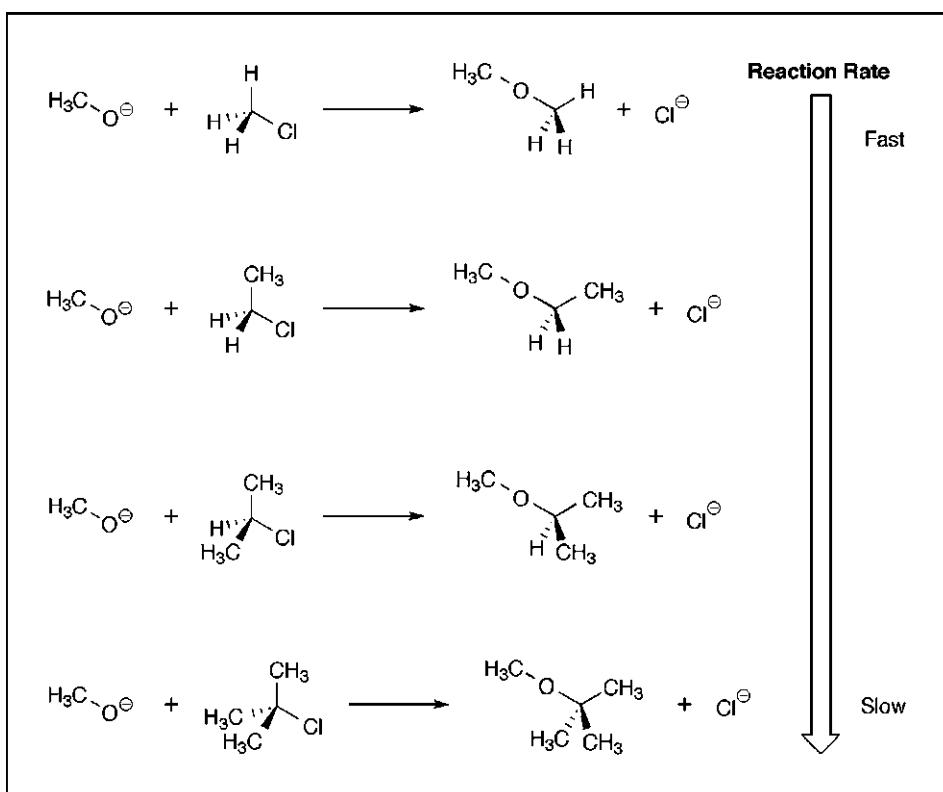
Because nucleophiles are attracted to sites of positive or partial positive charges, understanding the direction of polarity associated with a given bond serves three purposes. First, the site to which a given nucleophile is attracted is readily identified. Second, the spatial direction or trajectory of the reaction is readily identified. Lastly, the leaving group is readily identified. These are all graphically summarized in Scheme 4.5 using a different rendering of the S_N2 reaction illustrated in Scheme 4.3.

In Chapter 3, the relationship between nucleophiles and bases as influenced by **steric bulk** was addressed. What was not addressed is the complementary issue surrounding the accessibility of electrophilic (positively charged or partially positively charged) sites to nucleophiles. In fact, in the same way that nucleophilicity decreases with increasing steric bulk around the nucleophilic atom, the ability of a nucleophile to react with an electrophile also decreases with increasing steric bulk around the site of potential S_N2 reactions. This effect is illustrated in Scheme 4.6 using the reaction introduced in Scheme 4.3. As illustrated, successive introduction of methyl groups adjacent to the S_N2 reaction site results in *decreased reaction rates*.



Scheme 4.5 Understanding the direction of bond polarity allows identification of reaction site, trajectory of nucleophile, and identification of the leaving group.

Thus, when identifying sites where S_N2 reactions can occur, the following criteria must be met. First, S_N2 reactions occur at **tetrahedral** carbon atoms. Second, S_N2 reactions occur at molecular sites bearing the greatest degree of positive charge. Lastly, S_N2 reactions occur at sites that are **sterically accessible** to the incoming nucleophile.



Scheme 4.6 Steric bulk slows down reaction rates for S_N2 reactions.

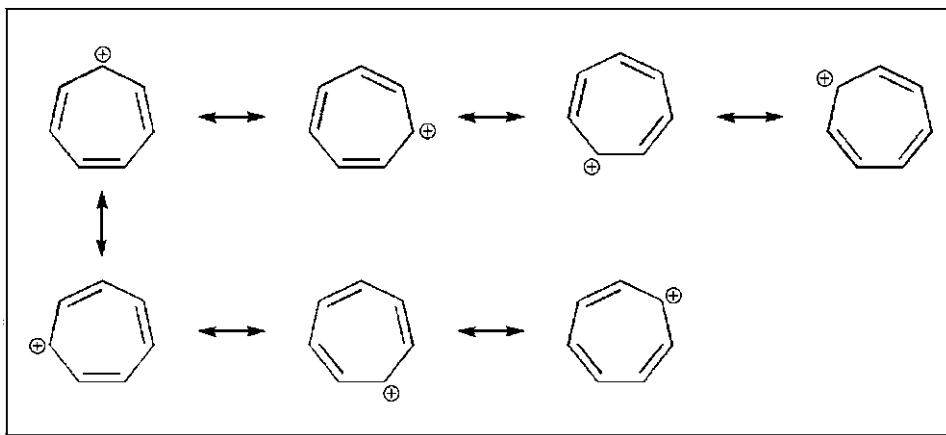
4.4 S_N2' REACTIONS

In the previous section, detailed discussions were presented illustrating conditions and criteria relevant to the initiation of S_N2 reactions. Furthermore, in previous chapters, the concept of resonance was introduced. When considering mechanistic organic chemistry, resonance is frequently recognized as contributing to the outcome of chemical reactions. In the following paragraphs, these contributions relative to S_N2 reactions are presented.

Resonance, as introduced in Chapter 2, explains stability of anions and rationalizes trends in pK_a values. However, resonance can also be used to rationalize the stability of **cations** (positively charged ions). As shown in Scheme 4.7, the stability of the cycloheptatriene cation is explained by its resonance forms. There is, of course, another reason for the stability of the cycloheptatriene cation, which relates to the principles of **aromaticity** and which will not be discussed in detail in this book.

As positively and negatively charged ions can be stabilized through resonance forms, so can species bearing partial positive charges and partial negative charges. As previously discussed, an electronegative atom attached to a carbon atom will induce a partial positive charge onto the carbon atom. As illustrated in Figure 4.4, when substituents possessing bond unsaturation are also attached to the partially positive carbon, the partial positive and partial negative charges are extended into the unsaturated system.

When partial positive charges are delocalized through **unsaturated** bonds, the result, as illustrated above, is the presence of multiple sites to which nucleophiles will be attracted. This principle is illustrated in Scheme 4.8 and explained through arrow pushing. As shown, when a nucleophile reacts with the terminal carbon atom, electrons from the double bond shift to displace the chloride ion. Since this is a **bimolecular nucleophilic substitution**, the mechanism type falls within the definition of S_N2 reactions. However, since this reaction occurs through a double bond, or an extended conjugated system, it is designated S_N2'. In the case of the example shown in Scheme 4.8, the product is formed through a combination of S_N2 and S_N2' mechanisms.



Scheme 4.7 Resonance forms can be used to rationalize the stability of cations adjacent to sites of bond unsaturation.

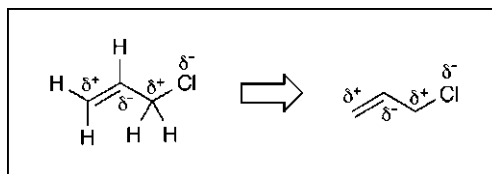
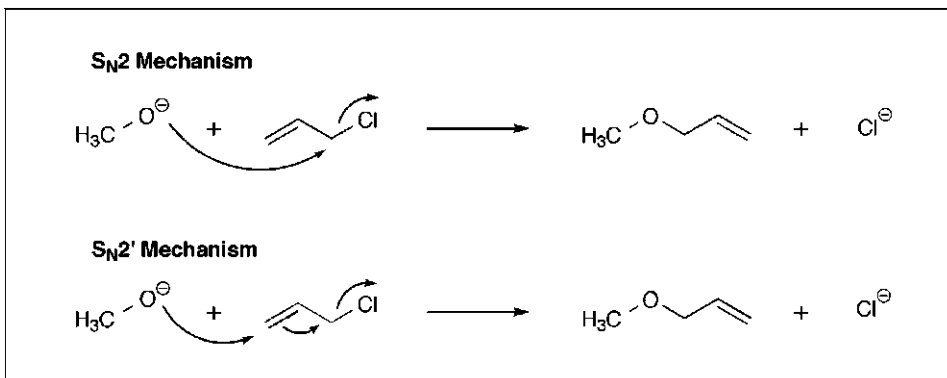
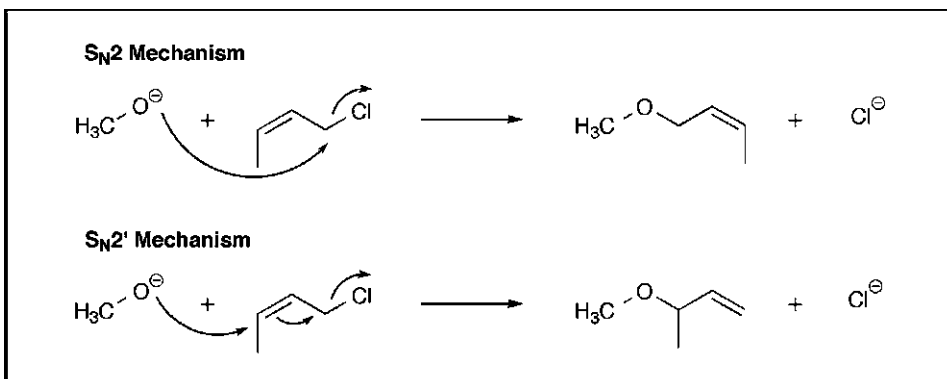


Figure 4.4 Partial charges can be delocalized through unsaturated bonds.



Scheme 4.8 Comparison of S_N2 and S_N2' reactions as explained with arrow pushing.

In the case of the reaction illustrated in Scheme 4.8, the product is not dependent upon which site the nucleophile is drawn to or which mechanism the reaction proceeds through. However, when the double bond possesses an additional substituent, product mixtures can form as illustrated in Scheme 4.9. In general, when predicting the outcome of reactions where both S_N2 and S_N2' reactions are possible, the major product will be dependent upon the steric constraints around the various reactive (or partially positively charged) sites. In cases where the nucleophile has comparable accessibility to electrophilic sites, product mixtures are usually the result.



Scheme 4.9 Competing S_N2 and S_N2' reaction mechanisms can lead to product mixtures.

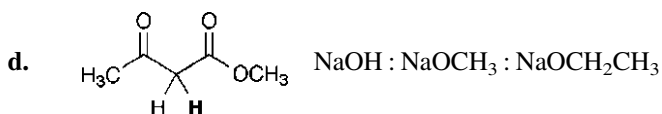
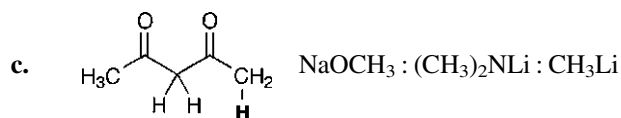
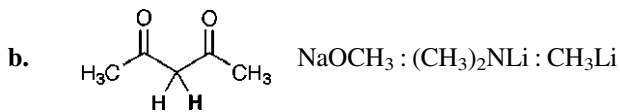
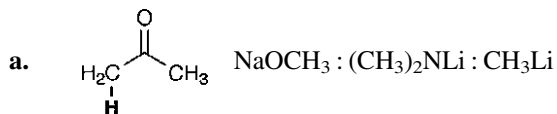
4.5 SUMMARY

In this chapter, S_N2 reaction mechanisms were defined and presented in the context of nucleophiles displacing leaving groups at electrophilic centers. Furthermore, the conditions required for S_N2 reactions to proceed were discussed as well as factors that influence the progression of such reactions. In this context, discussions of S_N2 reactions were extended into the related S_N2' reaction mechanisms.

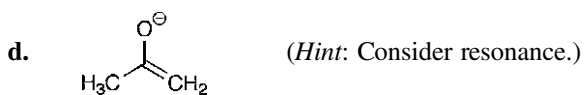
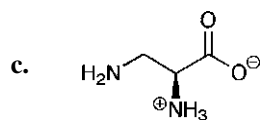
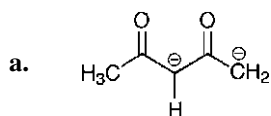
As the principles of this chapter, by nature, build upon those presented in previous chapters, the same will be for topics discussed in the remainder of this book. The study of organic chemistry is a progressive task with many overlapping principles. As should be apparent from topics discussed thus far, many of these principles reduce to the acid–base chemistry presented in the earliest chapters. This is also the case for the remaining topics presented herein.

PROBLEMS

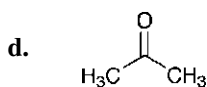
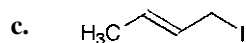
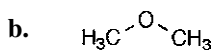
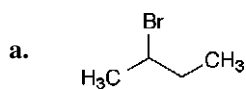
1. In many S_N2 reactions, the nucleophile is generated by deprotonation of an organic acid. For each molecule, choose the base best suited to completely remove the labeled proton. (Consider pK_a values and recognize that, in some cases, dianions should be considered.) Explain your answers.



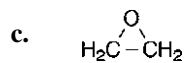
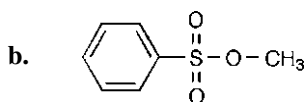
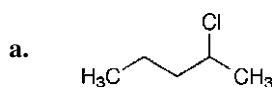
2. In predicting the course of S_N2 reactions, it is important to recognize groups most likely to act as nucleophiles. For each molecule, label the most nucleophilic site.



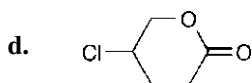
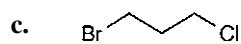
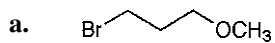
3. For each molecule, show the partial charges, bond polarity, and where a nucleophile is most likely to react.



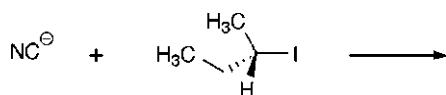
4. For each molecule, identify the leaving group assuming that H_3C^- is the nucleophile.



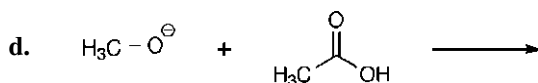
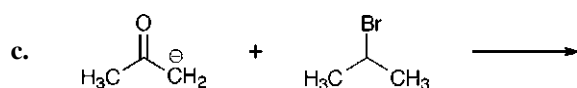
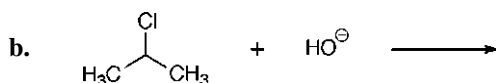
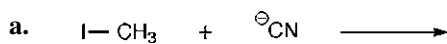
5. For each molecule, label the most likely leaving group. Explain your answers.

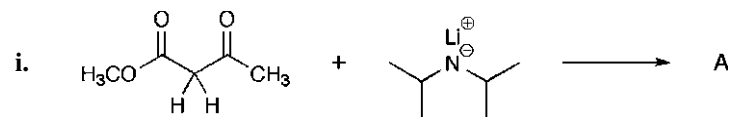
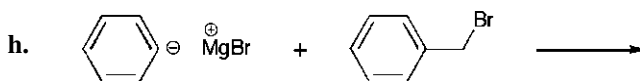
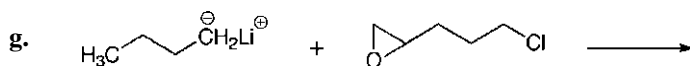
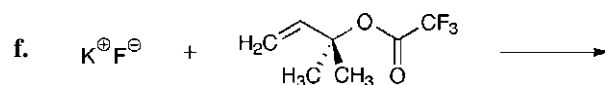
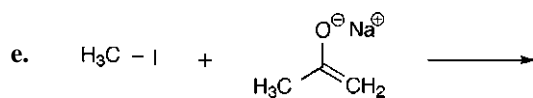


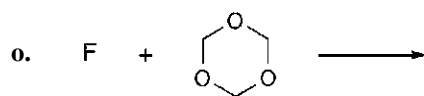
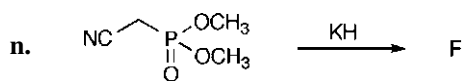
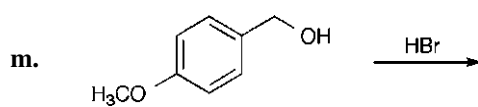
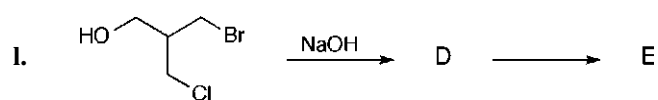
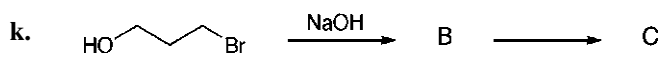
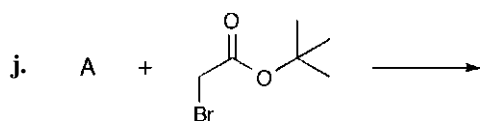
6. Detailed discussions focused on stereochemistry are not within the scope of this book. However, considering the products of typical S_N2 reactions, in addition to the transition state shown in Scheme 4.2, one may deduce the stereochemical course of this type of reaction. Predict the product of the following reaction and show the correct stereochemistry:



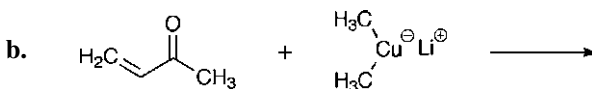
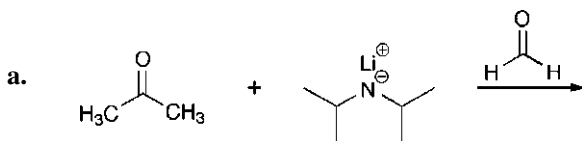
7. Predict the products of the following reactions by pushing arrows:



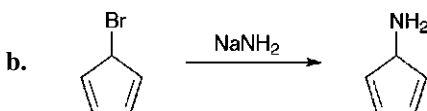
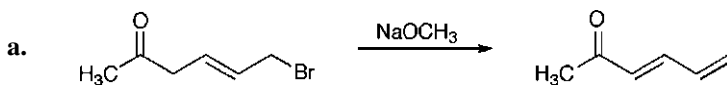


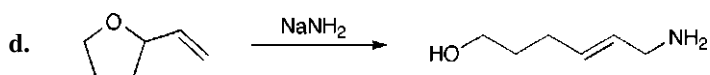
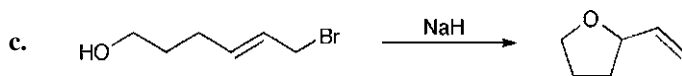


8. Addition reactions and conjugate addition reactions, to be discussed in Chapter 7, are related to S_N2 and S_N2' reactions, respectively. We can make these comparisons if we recognize that the carbonyl double bond contains a leaving group. Specifically, if a nucleophile adds to the carbon of a carbonyl, the carbonyl double bond becomes a carbon–oxygen single bond with a negative charge residing on the oxygen. Additionally, the trigonal-planar geometry of the carbonyl carbon is converted to tetrahedral geometry. With these points in mind, predict the products of the following reactions and explain your answers. For problem 8(b), the nucleophile is a methyl anion associated with the illustrated cuprate.



9. Propose a reasonable mechanism for each of the following reactions. Explain your answers by pushing arrows.





10. α,β -Unsaturated carbonyls are readily formed from the corresponding β -hydroxy ketones. Explain the product of the following reaction:

